REMARKS

As a convenience for the Examiner, a complete set of the pending claims is attached to this Amendment.

Since claims 77-150 are added, claims 45-150 will be pending following entry of this Amendment.

Several changes have been made in the specification to improve its form. These changes are essentially editorial in nature and do not constitute the addition of new matter. In particular, the specification amendments merely correct typographical and grammatical errors.

Claims 45, 48, 49, 53, 56, 58, 64, 65, 69, 70, 74, and 76 are amended to correct typographical errors, to sharpen the claim language, or to make cosmetic changes. The amendments to these claims are not narrowing amendments. The basis for the amended claim language may be found throughout the original specification and claims.

New claims 82-88, 111-117, 137-139, and 144-146, directed to embodiments, are supported by the specification and original claims, for example, at specification page 10, lines 1-2, and originally filed claim 6.

No new matter has been added.

Information Disclosure Statement

Attached to this Amendment is an Information Disclosure Statement including foreign documents. Applicants previously filed Information Disclosure Statement on September 27, 2002 including United States patent documents. Applicants respectfully request the Examiner to return a copy of the Form 1449 with his initials placed thereon, thereby indicating his review and consideration of the documents.

Suspension of Action

A Continued Prosecution Application and a Request for Suspension of Action for three months were filed on September 4, 2002. The Suspension of Action was approved on November 18, 2002, and, thus, is in effect until December 4, 2002. The Notice of Allowance issued in the present application on October 22, 2002 has been withdrawn.

Conclusion

The application is considered in good and proper form for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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LOR

PATENT
Attorney Docket No. 402090/SKYEPHARMA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MISHRA ET AL.

Application No. 09/376,487 Art Unit: 1617

Filed: August 18, 1999 Examiner: E. Webman

For: INJECTABLE AQUEOUS DISPERSIONS OF PROPOFOL

AMENDMENTS TO SPECIFICATION AND CLAIMS

Amendments to the paragraph beginning at page 2, line 16:

The compositions described by Glen and James in US Patent 4,056,635 and 4,452,817 are mixtures of propofol with surfactants such as ~~Cremophor-RH40~~ CREMOPHOR-RH40™ or ~~Cremophor-EL~~ CREMOPHOR-EL™ or ~~Tween-80~~ TWEEN-80™, in aqueous medium that may also contain ethanol or other pharmaceutically acceptable ingredients.

Amendments to the paragraph beginning at page 3, line 8:

Based on the above patents a propofol preparation for clinical use (PDR 1996) has been commercially available (~~Diprivan®~~ DIPRIVAN 1% Injection) which contains propofol dissolved in soybean oil and is stabilized with egg lecithin. Each milliliter of this formulation consists of 10 mg/mL of propofol, 100 mg/mL of soybean oil, 22.5 mg/mL of glycerol, 12mg/mL of egg lecithin, sodium hydroxide to adjust pH within 7 to 8.5 and sufficient quantity of water. Although clinically useful, this formulation requires the use of strict aseptic techniques during its handling due to the absence of antimicrobial preservatives and concomitant potential of microorganism growth. Indeed, many incidences of serious infection in human subjects have been linked to the use of the commercially available propofol formulation, ~~Diprivan®~~ DIPRIVAN (Nichols *et al.* (1995), Tessler *et al.* (1992), Ardulno *et al.* (1991), Sosis and Braverman (1993), Sosis *et al.* (1995), Crowther *et al.* (1996)).

Amendments to the paragraph beginning at page 3, line 20:

In order to minimize the chances of infection arising from the handling of the formulations of propofol during intravenous administration Jones and Platt have recently introduced a new propofol formulation, essentially based on the earlier composition with the added component of an antimicrobial preservative. This product is described by US patents 5,714,520; 5,731,355; and 5,731,356. The antimicrobial preservative that is added to the new formulation is disodium edetate. In US patent #5,714,520 it is claimed that addition of an amount of edetate limits bacterial growth to no more than a 10-fold increase as determined by the growth of each of *Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027 and *Candida albicans* ATCC 10231 for at least 24 hours as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said composition at approximately 50 colony forming units (CFU) per mL, at a temperature in the range 20-25°C, whereafter said aliquots are incubated at 20-25°C and are tested for viable counts of said organism after 24 hours, said amount of edetate being no more than 0.1% by weight of said composition.

Amendments to the paragraph beginning at page 4, line 11:

However, regardless of the presence of edetate as a preservative against growth of microorganisms, the product under US patent 5,714,520 (~~Diprivan~~® DIPRIVAN) is not considered an antimicrobially preserved product under USP standards by some authors, for instance, Sklar (1997). While in the quantity that is present, edetate may be effective against the growth of some types of organisms that are claimed in the ~~said~~ patent, it may not be so effective against a variety of other organisms that may be prevalent in the clinical situations where propofol is administered such as for example, *C. albicans* ATCC 10231 as noted in patent 5,714,520. Indeed, it was noted in patent 5,714,520 that the formulated propofol was not ~~bactericidal~~ microbicidal against *C. albicans* ATCC 10231 where an approximately 10-fold growth in the inoculum concentration was observed after 48 hours. This result points to the possibility of ineffectiveness of edetate as a preservative against growth of

microorganisms in Diprivan® formulation if challenged by other organisms than those cited above or by a higher load of organisms exceeding 100 CFU/mL. Indeed the addition of edetate to the formulation provides little in the way of real improvement. This "improved" formulation continues to be inferior, with respect to antibacterial effectiveness, to the invention described in the Haynes patent (US 5,637,625, see below).

Amendments to the paragraph beginning at page 5, line 8:

Many authors have reviewed the clinical usage of propofol formulations. For instance, Smith *et al.* (1994) describe that propofol injection has been used for producing and maintenance of ambulatory anesthesia, neurosurgical and pediatric anesthesia, for monitored anesthesia care, for intensive care sedation, and other clinical situations. Pain after injection of commercial formulations of propofol has been reported to occur in 28-90% of patients e.g., see reports by Mirakhur (1988), Stark *et al.* (1985), Mangar and Holak (1992). Even with low dose propofol administered for sedation, the incidence of pain can be 33-50%. (White and Negus, 1991; Ghouri *et al.* 1994). The mechanism responsible for the venous pain ~~on~~ upon propofol administration is unknown. The original excipient, ~~Cremophor EL~~ CREMOPHOR EL, of the earlier propofol preparation was initially thought to be the causative agent. However, there was no measurable reduction in pain after the change from the ~~Cremophor EL~~ CREMOPHOR EL based propofol formulation to the marketed soybean oil and lecithin based formulation (*e.g.*, see Mirakhur (1988), Stark *et al.* (1985), Mangar and Holak (1992). White and Negus, 1991; Ghouri *et al.* 1994). It is believed that the pain is a function of the drug itself, rather than the formulation (Smith *et al.* (1994)).

Amendments to the paragraph beginning at page 6, line 15:

While pain on injection may or may not be related to the injection-site tissue-irritation or the thrombogenicity of the administered formulation, these adverse reactions are still prevalent and symptoms continue to be reported in the clinical use of propofol. For instance, in the case of ~~Diprivan®~~ DIPRIVAN, these symptoms span the range of thrombosis and

phlebitis and include up to 17.6% incidences of burning/stinging or pain (PDR 1999, p. 3416).

Amendments to the paragraph beginning at page 7, line 4:

Alternative propofol formulations, that addressed some of the above-mentioned clinical problems associated with the commercial (~~Diprivan®~~ DIPRIVAN) or experimental (*e.g.*, those described by Babl et al. 1995, and Doenicke *et al.* 1996~~,~~ and 1997) propofol injectable products, have been taught by Haynes in ~~the~~ US patent 5,637,625. For instance, Haynes has recognized two problems associated with the use of large quantities of vegetable oil in a commercial formulation consisting of 1% propofol and 10% soybean oil:

(1) hyperlipidemia in patients undergoing long-term sedation in the intensive care unit (ICU), and

(2) the risk of bacterial contamination secondary to the high lipid content and lack of antimicrobial preservatives.

Amendments to the paragraph beginning at page 10, line 7:

At the surface of the water-insoluble matrix are amphiphilic agents that stabilize the dispersion and are of possible importance in affecting the degree of local reaction on injection. Examples of such amphiphilic agents include charged or uncharged phospholipids of natural sources, *e.g.*, egg or soy lecithin, or hydrogenated lecithin (*e.g.*, ~~phospholipon-90H~~ PHOSPHOLIPON-90H™ or ~~phospholipon-100H~~ PHOSPHOLIPON-100H™ from Nattermann), or synthetic phospholipids such as phosphatidylcholines or phosphatidylglycerols, pharmaceutically acceptable non-ionic surfactants such as poloxamers (~~pluronic~~ PLURONIC series of surfactants), poloxamines (~~tetronic~~ TETRONIC series of surfactants), polyoxyethylene sorbitan esters (*e.g.*, ~~Tween®~~ TWEEN™ series of surfactants), cholesterol, or other surface modifiers commonly used in pharmaceutical products, or combinations of these surface modifiers.

Amendments to the paragraph beginning at page 11, line 15:

Propofol is a liquid that is very poorly soluble in water. To manufacture stable injectable propofol formulations with the desired anti-microbial properties, low lipid content and low injection site reactivity and with little or no phase separation of the propofol during mixing or storage, it was found necessary to not only select an appropriate composition of the formulation but also use appropriate processing conditions. Examples of suitable processing conditions are those which provide intense mechanical agitation or high sheer, see for example the procedures described by Haynes (US patent 5,637,625). The formulation is conveniently prepared by the initial preparation of a lipophilic phase and an aqueous phase which are then mixed~~, however~~. However, those skilled in the art will appreciate that alternate approaches may be suitable and will readily be able to determine such approaches. For example, the unit processes as described briefly in the following paragraphs have proven suitable.

Amendments to the paragraph beginning at page 14, line 2:

> The circumference of the rat's tail was measured at approximately 2.5 inches proximal to the animal's body prior to the administration of the test formulation. This measurement served as a baseline value for assessing possible swelling of the tail upon intravenous administration of the formulation. On each study day, the treatment site was carefully examined to detect any reactions and the rat's tail circumference measured. Changes in the rat's tail circumference were evaluated by comparing Day 2 and Day 3 measurement to the baseline value obtained before administering the test articles.

Amendments to the paragraph beginning at page 15, line 17:

The formulations described in the present inventions were tested for their ability to inhibit the growth of microorganisms that are a potential source of most likely infections in the clinical situation. Growth of *Staphylococcus aureus* (ATCC 6538), *Escherichia coli*

(ATCC 8739 and ATCC 8454), *Pseudomonas aeruginosa* (ATCC 9027), *Candida albicans* (ATCC 10231), and *Aspergillus niger* (ATCC 16403) was measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of a formulation at approximately 1000 colony forming units (CFU) per mL, at a temperature in the range 20-25°C. The inoculated mixtures are incubated at 20-25°C. The viability of the microorganisms in the inoculated formulation is determined by counting the colonies of said organism after 24 and 48 hours, 7 days and other suitable ~~length~~ lengths of time.

Amendments to the paragraph beginning at page 16, line 7:

Unless otherwise specified, all parts and percentages reported herein are weight per unit weight (w/w), in which the weight in the denominator represents the total weight of the formulation. Diameters of dimensions are given in millimeters (mm = 10^{-3} meters), micrometers (μm = 10^{-6} meters), or nanometers (nm = 10^{-9} meters). Volumes are given in liters (L), milliliters (mL = 10^{-3} L), and microliters (μL = 10^{-6}L). Dilutions are by volume. All temperatures are reported in degrees Celsius. The compositions of the invention can comprise, consist essentially of, or consist of the materials set forth and the process or method can comprise, consist essentially of, or consist of the steps set forth with such materials.

Amendments to the table beginning at page 17, line 1:

Raw Material	Symbol	Source
~~1,2-Dimristoyl-sn-Glycero-3-Phosphocholine~~ 1,2-Dimyristoyl-sn-Glycero-3-Phosphatidylcholine	DMPC	Avanti Polar Lipids Inc., Alabaster, AL, US
~~1,2-Dimristoyl-sn-Glycero-3-[Phospho-rac-(1-glycerol))~~ 1,2-Dimyristoyl-sn-Glycero-3-[Phospho-rac-(1-glycerol)]	DMPG	Avanti Polar Lipids Inc., Alabaster, AL, US
Ethyl Oleate, NF	EO	Croda Leek Ltd, Staffordshire, UK
Glycerin, USP-FCC	GLY	J.T. Baker, Philipsburg, NJ, US
~~Lipoid E80-~~LIPOID E80™ (egg lecithin)	E80	Lipoid GmBH, Ludwigshafen
~~Lipoid EPC-~~LIPOID EPC™ (egg phosphatidylcholine)	EPC	Lipoid GmBH, Ludwigshafen
~~Lipoid SPC-~~LIPOID SPC™ (soy phosphatidylcholine)	SPC	Lipoid GmBH, Ludwigshafen
~~Lipoid SPC-3-~~LIPOID SPC-3™ (saturated soy phosphatidylcholine)	SSPC	Lipoid GmBH, Ludwigshafen
Mannitol, USP	MAN	J.T. Baker, Philipsburg, NJ, US
~~Miglyol 810-~~MIGLYOL 810™	M810	Hüls America, Piscatway, NJ, US
Propofol	PRO	Albemarle Corporation, Baton Rouge, LA, US
Soybean oil, USP	SO	Spectrum, New Brunswick, NJ, US
(D+) Alpha, alpha-Trehalose	TRE	Pfanstiehl Laboratories Inc, Waukegan, IL, US

Amendments to the paragraph beginning at page 17, line 4:

Table I summarizes some examples of the propofol formulations and their attributes with increasing amount of oil. The oil concentration of these formulations was increased by increasing the amount of ethyl oleate from 0.4% to 10%. Propofol concentration was kept at 1%. Amount of the phospholipid mixture (~~Lipoid E80-~~LIPOID E80 and DMPG) was adjusted with increasing amount of oil to obtain the formulations of good stability.

Amendments to the paragraph beginning at page 18, line 4:

Rat-tail swelling, an indicator of the tissue-irritation propensity of the formulation (see above), was found to decrease with increasing amount of oil. Formulation #1.4-1.6 with 4-10% ethyl oleate appear to result in unnoticeable rat-tail swelling. This result parallels the reported finding (Babl et al. 1995, and Doenicke *et al.* 1996, and 1997) that the use of higher amounts of oil in propofol preparations reduces the incidence of pain on injection possibly by a reduction of aqueous concentration of propofol. However, these authors have used a much higher amount (20%) of MCT and LCT mixture in their propofol formulations, and such formulations are expected to support the growth of microorganisms.

Amendments to Table I beginning on page 18, line 13:

Table I: Effect of increasing oil content of the formulation

Formulation ID	Propofol (%, w/w)	~~Lipoid E80~~ LIPOID E80 (%, w/w)	DMPG (%, w/w)	Ethyl Oleate (%, w/w)	Viscosity, cP	Rat Tail Swelling, at 48hr, mm	LDH (IU/L)
1.1	1	0.8	0.15	0.4	0.97	1.39	10918
1.2	1	0.8	0.10	1.0	1.08	0.6	10970
1.3	1	0.8	0.10	2.0	1.06	0.2	10300
1.4	1	1.0	0.25	4.0	1.04	0	3150
1.5	1	1.0	0.25	8.0	1.25	0	1290
1.6	1	1.0	0.25	10.0	1.34	0	770

Amendments to the paragraph beginning at page 20, line 11:

In Example 1 it was observed that by increasing the amount of oil from 0.4% to 10% or greater in the formulation, the tissue-irritation potential could be decreased. However, Example 2 indicates that this simplistic notion is not without limitation since in some cases merely increasing the amount of oil in the propofol formulation does not result in a less irritating formula. For instance, in formulation 2.26 the oil level is increased to 6% of ethyl oleate and in formulations 2.27 and 2.28 to 4% of ~~Miglyol 810~~ MIGLYOL 810, but these

formulations are still injection-site tissue-irritating, which is evident from the tail swelling values for these formulations.

Amendments to the paragraph beginning at page 21, line 11:

As established in Example 1 and again here in Example 2, merely increasing the oil level in ~~formulations~~ formulations did not result in decreasing the hemolytic potential, or ~~irritatation~~ irritation to the tissues at the site of injection. It appears that below a certain amount of oil (*e.g.*, <10%) the causative factors for improving the hemolytic potential or tissue irritation is a combination of various factors that originate from the specific composition. Thus, the non-irritating ~~formula~~ formulations that also have a low potential of hemolysis are characterized by various formulation components that provide the co-operative effects rendering the preferred formulations less irritating.

Amendments to the paragraph beginning at page 21, line 20:

Whether the formulations demonstrated the absence of thrombogenic irritation in rats or caused such irritation, all were examined for the microbicidal or microbistatic effectiveness as mentioned above of which some relevant results are summarized in Table III. Also presented in Table III are the microbicidal effectiveness test results for ~~Diprivan®~~ DIPRIVAN as a comparison.

Amendments to the footnote "Symbols and Note" at page 24, after Table II:Continued:

DMPC: dimyristoylphosphatidylcholine; DMPG: dimyristoylphosphatidylglycerol; E80: ~~Lipoid E80~~ LIPOID E80; EO: ethyl oleate; EPC: egg phosphatidylcholine; EPL: egg phospholipids; GLY: Glycerin; M810: ~~Miglyol 810~~ MIGLYOL 810; MAN=Mannitol; SO: soybean oil; SPC: soy phosphatidylcholine; SSPC: saturated soy phosphatidylcholine; TRE=Trehalose. Sources of these raw materials are mentioned above.

Amendments to Table III at page 25, line 1:

Table III: Log growth of certain microorganisms following an ~~intial~~ initial inoculation of 10^3 CFU/mL in presence of some propofol formulations.

Formulation ID of Example 2	Organism	*C. albicans* ATCC 10231			*P. aeruginosa* ATCC 9027			*E. coli* ATCC 8739			*A. niger* ATCC 16403			*S. aureus* ATCC 6538		
	~~Formulation~~ Plating Time	24 hr	48 hr	7 day	24 hr	48 hr	7 day	24 hr	48 hr	7 day	24 hr	48 hr	7 day	24 hr	48 hr	7 day
2.1	91.103	2.8	2.7	2.1	1.5	1.0	1.0	1.7	1.6	1.0	2.8	2.8	2.7	2.4	1.0	1.0
2.3	61.103	2.8	2.3	1.3	1.0	1.0	1.0	1.0	1.0	1.0	2.0	2.1	2.0	1.0	1.0	1.0
2.4	76.103	2.7	2.7	2.5	2.3	1.3	1.0	2.5	2.1	1.0	2.9	2.8	2.7	2.2	1.0	1.0
2.5	81.103	3.0	3.9	6.0	2.4	6.0	6.8	4.8	6.8	6.8	2.8	2.6	2.5	3.3	3.2	1.3
2.6	80.103	2.9	3.4	5.8	1.0	1.0	1.0	4.4	6.8	6.8	2.8	2.6	2.6	3.0	2.5	1.0
2.11	72.103	3.1	4.0	5.8	2.3	5.9	6.8	5.1	6.8	6.8	2.9	2.7	2.6	3.2	3.1	1.0
2.13	50.103-A	4.2	5.0	5.3	2.0	3.7	6.8	1.0	1.0	1.0	2.5	2.4	2.1	2.0	1.0	1.0
	~~Dipriven~~ DIPRIVAN	3.2	3.4	3.2	2.8	3.3	6.2	2.2	1.0	1.0	2.9	2.7	2.6	3.2	3.1	1.8

Amendments to the paragraph beginning at page 26, line 4:

As taught by Haynes (US patent #-5,637,625) it may be thought that increasing the amount of lipidic nutrients in the formulation would cause the formulation to support microorganism growth. However, it is surprising to note that by increasing the amount of oil (to up to 4-6%), formulations 2.1, 2.3 or 2.4 do not provide a medium for bacterial growth. It is worth noting that formulations 2.1, 2.3, and 2.4 were neither irritating, nor hemolytic while also inhibiting the growth of microorganisms. These non-irritating, non-hemolytic, and bactericidal or bacteristatic formulations are characterized as non-limiting examples of preferred compositions of this invention.

Amendments to Table IV beginning at page 26, line 16:

Table IV: Propofol formulations of high drug potency

	Formula 4.1	Formula 4.2	Formula 4.3
Propofol	5.0%	10.0%	10.0%
Cholesterol	0.25%	0.4%	0.5%
Cholesteryl oleate	---	4.0%	3.0%
~~Phospholipon 90H~~ PHOSPHOLIPON 90H	1.5%	1.8%	1.5%
DMPG	0.3%	0.3%	0.15%
Glycerol	2.5%	2.5%	2.5%
Sodium hydroxide	qs pH 6.9	qs pH 8.2	qs pH 7.0
Water	qs 100%	qs 100%	qs 100%

Amendments to the paragraph beginning at page 28, line 2:

Propofol formulations of this invention were compared for induction and duration of anesthesia in rats with the reference commercial formulation, ~~Diprivan®~~ DIPRIVAN® (1%) and ~~Diseprivan®~~ DISOPRIVAN® (2%). Following 12.5 mg/kg single bolus intravenous injection of these formulations in rats, the time for loss of consciousness and righting response time were measured as mentioned above in the experimental method section. The results are summarized in Table V illustrating the efficacious characteristic of these formulations.

Amendments to Table V beginning at page 28, line 8:

Table V: Pharmacodynamic Parameters

Formulation ID	Number of Rats	Average Anesthesia Induction Time (sec)	Average Righting Response Time (min)
2.1	9	24.4	14.9
2.2	4	31.0	16.2
2.3	4	48.0	16.4
2.4	9	32.7	15.8
2.5	9	27.2	19.2
2.6	9	38.4	19.4
2.7	4	24.0	17.3
2.8	4	23.8	16.7
2.9	3	67.3	11.9
2.10	4	34.8	16.3
2.11	8	40.5	18.6
2.12	4	36.3	13.7
~~Diprivan®~~ DIPRIVAN (1% with EDTA)	4	20.0	14.6

Amendments to existing claims:

45. (Amended) A composition of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm, the dispersion consisting essentially of

(a) between about 1% to about 15% of propofol;

(b) between about 1% to about 8% of a ~~propofol soluble~~ propofol-soluble diluent;

(c) between about 0.5% to about 5% of a surface stabilizing amphiphilic agent; and

(d) a pharmaceutically acceptable water-soluble polyhydroxy additive that acts as a tonicity modifier; and

(e) water;

(f) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise,

wherein the ~~composition~~ dispersion

prevents microbial growth, defined as no more than 0.5 log increase from the initial inoculum, of each of *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans,* and *Aspergillus niger* for at least 7 days as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said ~~composition~~ dispersion at approximately 1000 colony forming units per mL, at a temperature in the range 20-25°C, whereafter said aliquots are incubated at 20-25°C and are tested for viability of the microorganisms in the inoculated ~~composition~~ dispersion as determined by counting the colonies of said organism after 24, 48 hours and 7 days; and

results in no irritation at the site of injection as evidenced by a test wherein said ~~composition~~ dispersion is administered as a single daily bolus injection of 12.5 mg/kg, given on the basis of body weight, for 2 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48 hours post injection.

48. (Amended) The composition of claim 45, wherein the ratio of propofol to the ~~amount of~~ propofol-soluble diluent is from about 1:3 to about 1:0.5.

49. (Amended) The composition of claim 45, wherein the ratio of propofol to the ~~amount of~~ propofol-soluble diluent is from about 1:2 to about 1:1.

53. (Amended) The composition of claim 45, wherein the pharmaceutically acceptable water-soluble polyhydroxy additive provides the ~~propofol containing~~ propofol-containing dispersion or composition with an osmolality of about 250 to about 700 milliosmolal.

56. (Amended) An injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm,

the dispersion being capable of inhibiting the growth of microorganisms and consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, water, and ~~the aqueous phase comprising~~ a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents and causing no irritation at the site of injection.

58. (Amended) The dispersion of claim 56, where the propofol and amphiphilic agent are present in a ratio of about 1:0.8 to about 1:2.5 of propofol to amphiphilic agent.

64. (Amended) The ~~diluent~~ dispersion of claim 63, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

65. (Amended) The dispersion of claim 56, ~~wherein the water-insoluble matrix~~ which contains about 2% to about 10% of propofol.

69. (Amended) The dispersion of claim 56, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of ~~,2-dimristoyl-sn-glycero-3-phosphocholine, 1,2-dimristoyl-sn-glycero-3-~~ 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine, 1,2-dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], egg lecithin, egg phosphatidylcholine, soy phosphatidylcholine, saturated soy phosphatidylcholine, soy lecithin, dimyristoylphosphatidylcholine, and dimyristoylphosphatidylglycerol.

70. (Amended) The dispersion of claim 56 that elicits an anesthetic effect in a warm-blooded animal and human ~~subjects~~ subject upon intravenous administration.

74. (Amended) The dispersion of claim 56 that contains a pharmaceutically acceptable water-soluble polyhydroxy ~~additive that provides~~ tonicity modifier in an amount so as to provide an osmolality of about 250 to about 700 milliosmolal.

76. (Amended) The dispersion of claim 56~~,~~ that has a viscosity from about 2 to about 5 centipoise.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MISHRA ET AL.

Application No. 09/376,487 Art Unit: 1617

Filed: August 18, 1999 Examiner: E. Webman

For: INJECTABLE AQUEOUS DISPERSIONS OF PROPOFOL

PENDING CLAIMS AFTER AMENDMENTS

45. A composition of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm, the dispersion consisting essentially of

(a) between about 1% to about 15% of propofol;

(b) between about 1% to about 8% of a propofol-soluble diluent;

(c) between about 0.5% to about 5% of a surface stabilizing amphiphilic agent; and

(d) a pharmaceutically acceptable water-soluble polyhydroxy additive that acts as a tonicity modifier; and

(e) water;

(f) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise,

wherein the dispersion

prevents microbial growth, defined as no more than 0.5 log increase from the initial inoculum, of each of *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans,* and *Aspergillus niger* for at least 7 days as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said dispersion at approximately 1000 colony forming units per mL, at a temperature in the range 20-25°C, whereafter said aliquots are incubated at 20-25°C and are tested for viability of the microorganisms in the inoculated dispersion as determined by counting the colonies of said organism after 24, 48 hours and 7 days; and

results in no irritation at the site of injection as evidenced by a test wherein said dispersion is administered as a single daily bolus injection of 12.5 mg/kg, given on the basis of body weight, for 2 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48 hours post injection.

46. The composition of claim 45, wherein the surface stabilizing amphiphilic agent is a surface modifier selected from the group consisting of ionizable phospholipid, non-ionizable phospholipid, a mixture of ionizable phospholipid and cholesterol, a mixture of non-ionizable phospholipid and cholesterol, and mixtures thereof.

47. The composition of claim 45, wherein the propofol-soluble diluent is selected from the group consisting of a synthetic fatty acid triglyceride, a natural fatty acid triglyceride, and mixtures thereof.

48. The composition of claim 45, wherein the ratio of propofol to the propofol-soluble diluent is from about 1:3 to about 1:0.5.

49. The composition of claim 45, wherein the ratio of propofol to the propofol-soluble diluent is from about 1:2 to about 1:1.

50. The composition of claim 45, wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

51. The composition of claim 50, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

52. The composition of claim 45, wherein the composition contains about 2% to about 10% of propofol.

53. The composition of claim 45, wherein the pharmaceutically acceptable water-soluble polyhydroxy additive provides the propofol-containing dispersion or composition with an osmolality of about 250 to about 700 milliosmolal.

54. The composition of claim 53, wherein the osmolality is about 300 to about 500 milliosmolal.

55. The composition of claim 45, wherein the viscosity is from about 2 to about 5 centipoise.

56. An injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm, the dispersion being capable of inhibiting the growth of microorganisms and consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, water, and a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents and causing no irritation at the site of injection.

57. The dispersion of claim 56, where the propofol and diluent are present in a ratio of about 1:4 to about 1:0.1 of propofol to diluent.

58. The dispersion of claim 56, where the propofol and amphiphilic agent are present in a ratio of about 1:0.8 to about 1:2.5 of propofol to amphiphilic agent.

59. The dispersion of claim 56 that has a viscosity of from about 0.8 to about 15 centipoise.

60. The dispersion of claim 56, wherein the propofol-soluble diluent is selected from the group consisting of a pharmaceutically acceptable saturated fatty acid triglyceride, a pharmaceutically acceptable unsaturated fatty acid triglyceride, and mixtures thereof.

61. The dispersion of claim 56, wherein the propofol-soluble diluent is selected from the group consisting of pharmaceutically acceptable esters of medium chain fatty acids, pharmaceutically acceptable esters of long chain fatty acids, pharmaceutically acceptable triglycerides of medium chain fatty acids, and mixtures thereof.

62. The dispersion of claim 56, wherein the propofol-soluble diluent is selected from the group consisting of isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol, and mixtures thereof.

63. The dispersion of claim 56, wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

64. The dispersion of claim 63, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

65. The dispersion of claim 56, which contains about 2% to about 10% of propofol.

66. The dispersion of claim 56, wherein the surface stabilizing amphiphilic agent is a surface modifier selected from the group consisting of ionizable phospholipid, non-ionizable phospholipid, a mixture of ionizable phospholipid and cholesterol, a mixture of non-ionizable phospholipid and cholesterol, and mixtures thereof.

67. The dispersion of claim 56, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of charged phospholipid of natural sources, uncharged phospholipid of natural sources, hydrogenated lecithin, a synthetic phospholipid, a poloxamer, a poloxamine, a polyoxyethylene sorbitan ester, and mixtures thereof.

68. The dispersion of claim 56, wherein the surface stabilizing amphiphilic agent is a combination of cholesterol and one or more charged or uncharged phospholipid of natural sources, hydrogenated lecithin, or synthetic phospholipids.

69. The dispersion of claim 56, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine, 1,2-dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], egg lecithin, egg phosphatidylcholine, soy phosphatidylcholine, saturated soy phosphatidylcholine, soy lecithin, dimyristoylphosphatidylcholine, and dimyristoylphosphatidylglycerol.

70. The dispersion of claim 56 that elicits an anesthetic effect in a warm-blooded animal and human subject upon intravenous administration.

71. The dispersion of claim 56, wherein the tonicity modifier is selected from the group consisting of sucrose, dextrose, trehalose, mannitol, lactose, glycerol, and mixtures thereof.

72. The dispersion of claim 56 that is isotonic with blood.

73. The dispersion of claim 56 that is suitable for intravenous injection.

74. The dispersion of claim 56 that contains a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier in an amount so as to provide an osmolality of about 250 to about 700 milliosmolal.

75. The dispersion of claim 74, wherein the osmolality is about 300 to about 500 milliosmolal.

76. The dispersion of claim 56 that has a viscosity from about 2 to about 5 centipoise.

77. The composition of claim 45, wherein propofol is present in an amount of about 2% to 5% by weight of the dispersion.

78. The composition of claim 77, wherein propofol is present in an amount of about 2% by weight of the dispersion.

79. The composition of claim 45, wherein the polyhydroxy additive is present in an amount of about 2.5% to about 20% by weight of the dispersion.

80. The composition of claim 45, wherein the polyhydroxy additive is mannitol.

81. The composition of claim 80, wherein mannitol is present in an amount of about 5.5% by weight of the dispersion.

82. The composition of claim 45, wherein the propofol-soluble diluent is a medium chain triglyceride.

83. The composition of claim 45, wherein the propofol-soluble diluent is a mixture of medium-chain triglycerides.

84. The composition of claim 82, wherein the medium-chain triglyceride is a triglyceride of medium-chain fatty acids of synthetic or natural origin.

85. The composition of claim 82, wherein the medium-chain triglyceride is present in an amount of 2% to 6% by weight of the dispersion.

86. The composition of claim 85, wherein the medium-chain triglyceride is present in an amount of 2% to 4% by weight of the dispersion.

87. The composition of claim 86, wherein the medium-chain triglyceride is present in an amount of 4% by weight of the dispersion.

88. The composition of claim 83, wherein the mixture of medium-chain triglycerides is present in an amount of 4% by weight of the dispersion.

89. The composition of claim 45, wherein the amphiphilic agent is egg lecithin.

90. The composition of claim 89, wherein the egg lecithin is present in an amount of about 1% to about 7% by weight of the dispersion.

91. The composition of claim 90, wherein the egg lecithin is present in an amount of about 1% to 3% by weight of the dispersion.

92. The composition of claim 91, wherein the egg lecithin is present in an amount of 1.6% by weight of the dispersion.

93. The composition of claim 89, wherein the egg lecithin contains not less than 98% phosphatidyl choline.

94. The composition of claim 45, which includes anionic dimyristoylphosphatidyl glycerol.

95. The composition of claim 94, wherein the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.05% to 0.25% by weight of the dispersion.

96. The composition of claim 95, wherein the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.1% by weight of the dispersion.

97. The composition of claim 45, which includes egg lecithin and anionic dimyristoylphosphatidyl glycerol.

98. The composition of claim 97, wherein the egg lecithin is present in an amount of about 1% to 3% by weight of the dispersion and the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.05% to 0.25% by weight of the dispersion.

99. The composition of claim 98, wherein the egg lecithin is present in an amount of 1.6% by weight of the dispersion and the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.1% by weight of the dispersion.

100. The composition of claim 45, wherein the pH of the composition is about 4 to about 9.

101. The composition of claim 100, wherein the pH of the composition is about 5 to about 8.

102. The composition of claim 45, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

103. The composition of claim 45, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

104. The composition of claim 102, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

105. The composition according to claim 45, wherein the dispersion is steam sterilizable.

106. The dispersion of claim 56, wherein propofol is present in an amount of about 2% to 5% by weight of the dispersion.

107. The dispersion of claim 106, wherein propofol is present in an amount of about 2% by weight of the dispersion.

108. The dispersion of claim 56, wherein the polyhydroxy tonicity modifier is present in an amount of 2.5% to about 20% by weight of the dispersion.

109. The dispersion of claim 56, wherein the polyhydroxy tonicity modifier is mannitol.

110. The dispersion of claim 109, wherein mannitol is present in an amount of about 5.5% by weight of the dispersion.

111. The dispersion of claim 56, wherein the propofol-soluble diluent is a medium-chain triglyceride.

112. The dispersion of claim 56, wherein the propofol-soluble diluent is a mixture of medium-chain triglycerides.

113. The dispersion of claim 111, wherein the medium-chain triglyceride is a triglyceride of medium chain fatty acids of synthetic or natural origin.

114. The dispersion of claim 111, wherein the medium-chain triglyceride is present in an amount of 2% to 6% by weight of the dispersion.

115. The dispersion of claim 114, wherein the medium-chain triglyceride is present in an amount of 2% to 4% by weight of the dispersion.

116. The dispersion of claim 115, wherein the medium-chain triglyceride is present in an amount of 4% by weight of the dispersion.

117. The dispersion of claim 112, wherein the mixture of medium-chain triglycerides is present in an amount of 4% by weight of the dispersion.

118. The dispersion of claim 56, wherein the amphiphilic agent is egg lecithin.

119. The dispersion of claim 118, wherein the egg lecithin is present in an amount of about 1% to about 7% by weight of the dispersion.

120. The dispersion of claim 118, wherein the egg lecithin is present in an amount of about 1% to 3% by weight of the dispersion.

121. The dispersion of claim 120, wherein the egg lecithin is present in an amount of 1.6% by weight of the dispersion.

122. The dispersion of claim 118, wherein the egg lecithin contains not less than 98% phosphatidyl choline.

123. The dispersion of claim 56, which includes anionic dimyristoylphosphatidyl glycerol.

124. The dispersion of claim 123, wherein the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.05% to 0.25% by weight of the dispersion.

125. The dispersion of claim 124, wherein the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.1% by weight of the dispersion.

126. The dispersion of claim 56, which includes egg lecithin and anionic dimyristoylphosphatidyl glycerol.

127. The dispersion of claim 126, wherein the egg lecithin is present in an amount of about 1% to 3% by weight of the dispersion and the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.05% to 0.25% by weight of the dispersion.

128. The dispersion of claim 127, wherein the egg lecithin is present in an amount of 1.6% by weight of the dispersion and the anionic dimyristoylphosphatidyl glycerol is present in an amount of 0.1% by weight of the dispersion.

129. The dispersion of claim 56, wherein the pH of the dispersion is about 4 to about 9.

130. The dispersion of claim 129, wherein the pH of the dispersion is about 5 to about 8.

131. The dispersion of claim 56, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

132. The dispersion of claim 56, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

133. The dispersion of claim 131, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

134. The dispersion of claim 56, wherein the dispersion is steam sterilizable.

135. The dispersion of claim 70, wherein the anesthetic effect comprises at least one of producing and maintaining ambulatory anesthesia, neurosurgical anesthesia, pediatric anesthesia, monitored anesthetic care, intensive care sedation, chronic sedation, general anesthesia, low dose sedation, and long-term sedation.

136. A composition of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm, the dispersion consisting essentially of:

(a) propofol in an amount from about 1% to about 15% by weight of the dispersion;

(b) a propofol-soluble diluent in an amount from about 1% to about 8% by weight of the dispersion;

(c) a surface stabilizing amphiphilic agent in an amount from about 0.5% to about 5% by weight of the dispersion;

(d) a pharmaceutically acceptable water-soluble polyhydroxy additive; and

(e) water;

(e) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5 and the composition has a viscosity of about 0.8 to about 15 centipoise;

wherein the dispersion prevents microbial growth of no more than 0.5 log increase from the initial inoculum, of any one of *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans,* and *Aspergillus niger* for at least 7 days as measured by a test wherein a washed suspension of the microbe is added to an aliquot of said dispersion at approximately 1000 colony forming units per mL, at a temperature in the range of 20-25°C, whereafter said aliquot is incubated at 20-25°C and tested for viability of the

microbe in the inoculated dispersion as determined by counting the colonies of the microbe after 24 hours, 48 hours, and 7 days; and

wherein the dispersion results in no irritation at the site of injection as evidenced by a test wherein said dispersion is administered as a single daily bolus injection of 12.5 mg/kg, given on the basis of body weight, for 2 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48 hours post injection.

137. A composition of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm, the dispersion consisting essentially of:

(a) propofol in an amount of about 2% by weight of the dispersion;

(b) a medium-chain triglyceride in an amount of 4% by weight of the dispersion;

(c) egg lecithin in an amount of 1.6% by weight of the dispersion;

(d) anionic dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion;

(e) mannitol in an amount of 5.5% by weight of the dispersion; and

(f) water.

138. A composition of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm, the dispersion consisting essentially of:

(a) propofol in an amount of about 2% by weight of the dispersion;

(b) a mixture of medium-chain triglycerides in an amount of 4% by weight of the dispersion;

(c) egg lecithin in an amount of 1.6% by weight of the dispersion;

(d) anionic dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion;

(e) mannitol in an amount of 5.5% by weight of the dispersion; and

(f) water.

139. The composition of claim 137, wherein the medium chain triglyceride is of synthetic or natural origin.

140. The composition of claim 137, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

141. The composition of claim 137, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

142. The composition of claim 140, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

143. The composition of claim 137, wherein the dispersion is steam sterilizable.

144. An injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm capable of inhibiting the growth of microorganisms, the dispersion consisting essentially of:

propofol in an amount of about 2% by weight of the dispersion;

a medium-chain triglyceride in an amount of 4% by weight of the dispersion;

egg lecithin in an amount of 1.6 % by weight of the dispersion;

anionic dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion; and

mannitol in an amount of 5.5% by weight of the dispersion;

wherein the dispersion is devoid of additional bactericidal or bacteriostatic preservative agents and causes no irritation at the site of injection.

145. An injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix having a mean diameter of about 50 nm to about 1000 nm capable of inhibiting the growth of microorganisms, the dispersion consisting essentially of:

propofol in an amount of about 2% by weight of the dispersion;

a mixture of medium-chain triglycerides in an amount of 4% by weight of the dispersion;

egg lecithin in an amount of 1.6 % by weight of the dispersion;

anionic dimyristoylphosphatidyl glycerol in an amount of 0.1% by weight of the dispersion; and

mannitol in an amount of 5.5% by weight of the dispersion;

wherein the dispersion is devoid of additional bactericidal or bacteriostatic preservative agents and causes no irritation at the site of injection.

146. The dispersion of claim 144, wherein the medium chain triglyceride is of synthetic or natural origin.

147. The dispersion of claim 144, wherein the dispersion is sealed in a glass vial under nitrogen with a stopper.

148. The composition of claim 144, wherein the dispersion is sealed in a glass vial under an inert atmosphere with a stopper.

149. The dispersion of claim 147, wherein the dispersion is filled to about 70-90% volume capacity in the glass vial.

150. The composition of claim 144, wherein the dispersion is steam sterilizable.